Systemic effects of formoterol and salmeterol: a dose-response comparison in healthy subjects

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Abstract

Background—The main adverse effects of inhaled long acting β_2 agonists relate to their systemic activity. The systemic effects seen over eight hours after inhalation of three doses of salmeterol and formoterol were therefore compared in normal subjects.

Methods—A double blind, randomised, crossover study was carried out in 16 healthy subjects who inhaled formoterol 24, 48 and 96 µg (via Turbuhaler®), salmeterol 100, 200 and 400 µg (via Diskhaler®), or placebo on separate days. Heart rate, systolic and diastolic blood pressure, and plasma potassium and glucose concentrations were measured for eight hours following each drug and mean values were used to plot the time course of change after each dose. Mean maximum (or minimum) absolute values were used to construct dose-response curves to calculate the relative dose potency of the two drugs. Lunch was taken after the four hour readings and, since this caused additional changes to the main outcome measures, data from the first four hours are also presented in a post hoc analysis.

Results—Both salmeterol and formoterol caused an early dose dependent increase in heart rate and glucose concentrations and a fall in diastolic blood pressure and plasma potassium concentration; formoterol also caused an early increase in systolic blood pressure. The cardiovascular effects occurred more rapidly than the metabolic effects and the response to formoterol was faster than that of salmeterol, apart from the glycaemic response. The effects of salmeterol were slightly more prolonged than those of formoterol, although some dose related effects were apparent at eight hours with both drugs. The relative dose potency for formoterol compared with salmeterol at four and eight hours for the different end points excluding systolic blood pressure ranged from 1.6 to 7.0 after adjusting for baseline values. Relative dose potencies (95% CI) for maximum heart rate and plasma potassium concentrations were 4.1 (3.0 to 5.6) and 5.8 (4.1 to 8.6) over four hours and 2.4 (1.2 to 3.8) and 3.0 (1.2 to 5.7) over eight hours.

Conclusions—Formoterol and salmeterol cause dose related changes in heart rate, diastolic blood pressure, and plasma glucose and potassium concentrations. Formoterol has a more rapid onset for most end points whereas salmeterol has slightly more prolonged activity. Both drugs have a relatively modest therapeutic window. The relative dose potencies of the two drugs for the main end points were similar to the fourfold difference in recommended doses. Some differences in the pharmacological profile of the two drugs emerged and are as yet unexplained.

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Twice daily administration of the two long acting β_2 agonists, formoterol and salmeterol, produces sustained bronchodilatation and a reduction in symptoms compared with both placebo and regular short acting β_2 agonists.[1–7] The benefit has been maintained for up to a year[5–7] and both drugs are generally well tolerated when given twice daily in recommended doses. Inhalation of 400 µg salmeterol, four times the maximum dose recommended, caused marked changes in heart rate, QTc interval, and plasma potassium and glucose concentrations in both normal and asthmatic subjects,[8–11] and salmeterol has had a relatively modest therapeutic window in dose response studies.[9–11] Inhaled formoterol also causes dose related systemic effects,[12–17] but how they compare with those seen with salmeterol has not been determined.

The main adverse effects of β_2 agonists relate to their systemic activity and some patients have trouble from tremor or palpitations. A drug with a larger therapeutic window would be expected to cause fewer adverse effects and have a greater safety margin, particularly if taken in higher doses. Formoterol has a more rapid onset of action than salmeterol[18 19] and can be used now for relief of symptoms, in addition to regular use, in doses up to 54 µg/day. We have therefore compared the time course for the systemic effects of three doses of salmeterol and formoterol in healthy non-asthmatic subjects. Dose-response curves for the mean maximum (or minimum) systemic end points were plotted for each drug so that equivalent doses could be determined and the relative dose potency assessed.

Methods

SUBJECTS

Eighteen subjects were recruited although two withdrew after the first study visit for personal reasons and are not considered further; they had received formoterol 24 µg and 48 µg, respectively, but had not reported adverse

Table 1   Mean (SE) baseline values of heart rate, QTc interval, systolic and diastolic blood pressure, plasma potassium concentration and plasma glucose concentration on the seven study days

	Formoterol			Salmeterol			Placebo
	24 µg	*48 µg*	*96 µg*	*100 µg*	*200 µg*	*400 µg*	
Heart rate (bpm)	55.6 (1.7)	56 (1.6)	54.8 (1.4)	55.6 (1.4)	56 (1.7)	55.9 (1.4)	56 (1.4)
QTc interval (ms)	400 (3.5)	397 (3.6)	397 (3.6)	400 (3.2)	396 (4.1)	403 (2.8)	398 (3.1)
Systolic BP (mmHg)	115 (3.1)	118 (3.3)	116 (3.6)	114 (2.5)	114 (2.7)	115 (3.5)	113 (3)
Diastolic BP (mmHg)	72 (2.6)	76 (2)	77 (2.7)	74 (2.1)	74 (1.8)	75 (2.6)	74 (2.4)
Plasma K$^+$ (mmol/l)	4.1 (0.1)	4 (0.1)	4 (0.1)	4. (0.1)	4 (0.1)	4 (0.1)	4.1 (0.1)
Plasma glucose (mmol/l)	5.3 (0.2)	5.3 (0.2)	5.2 (0.1)	5.4 (0.2)	5.3 (0.2)	5.3 (0.1)	5.4 (0.1)

effects during the study. Subjects had to be aged 18–60, healthy as determined by medical history, physical examination and laboratory screening tests, within 15% of their ideal body weight (Metropolitan Life Insurance), and currently a non-smoker or smoking fewer than 10 cigarettes a day. No medication other than occasional paracetamol or the oral contraceptive pill was allowed during the four weeks before the study. Women of childbearing age were required to have adequate contraception and a negative pregnancy test on each study day. All subjects gave written informed consent to the study which was approved by the University of Nottingham Medical School ethics committee.

MEASUREMENTS

All pharmacodynamic measurements were made with the subjects semirecumbent and resting for at least 30 minutes. Heart rate and QTc interval (QT interval corrected for heart rate) were measured by a 12-channel electrocardiograph (Marquette MAC II, Marquette Electronics Inc, Milwaukee, USA) programmed to calculate mean values from five consecutive R–R intervals. Systolic and diastolic blood pressure were measured by an automated digital sphygmomanometer (HEM-705CP, Omron Corporation, Tokyo, Japan) with a standard cuff width. Venous plasma samples were stored at –70°C and analysed as a single batch at the end of the study. Plasma potassium and glucose concentrations were measured by ion selective electrodes and hexokinase assay, respectively (both Olympus AU600, Olympus Optical Company Ltd, Eastleigh, UK).

PROTOCOL

This was a double blind, placebo controlled, seven way, crossover study with the treatment order determined by random code. Subjects attended an initial screening visit when a medical history, physical examination, and laboratory screening test were carried out and they were taught the correct use of the inhalers. They were asked to take no medication during the study period other than paracetamol for analgesia if required and the oral contraceptive pill if relevant. Subjects agreed that they would refrain from strenuous exercise and alcohol for 24 hours before each visit and from smoking, food and beverages (apart from water) from midnight. Subjects were transported to and from the department and lunch was provided four hours after dosing.

Subjects attended the department at the same time on seven mornings with a washout period of at least 72 hours between visits. An intravenous cannula (Y-can, Simcare, Lancing, UK) was inserted into a forearm vein and kept patent with heparinised saline. An automated sphygmomanometer cuff was applied to the opposite arm. Electrocardiographic measurements and blood pressure were recorded at five minute intervals until three consecutive readings of heart rate and blood pressure were within 10 beats per minute and 10 mm Hg, respectively. Venous blood (5 ml) was taken for measurement of baseline plasma potassium and glucose concentrations before dosing.

Once baseline measurements were stable, subjects inhaled placebo, salmeterol (100, 200 or 400 µg) or formoterol (24, 48 or 96 µg) from a set of six inhalers (two Turbuhaler®, four Diskhaler®) containing placebo or active drug (doses refer to the metered dose leaving the inhaler). A separate set of six inhalers was used for each study day for each subject. One inhalation from the Turbuhaler® contained formoterol 6 or 12 µg or placebo while one inhalation from the Diskhaler® contained salmeterol 50 µg or placebo. Subjects took four inhalations from each Turbuhaler® and two inhalations from each of the four Diskhalers® at a rate of one inhalation per 15 seconds. Each inhalation was from functional residual capacity to total lung capacity followed by a 10 second breath hold.

Timing started immediately after the final inhalation when subjects returned to a semirecumbent position with encouragement to relax. For the first nine minutes the heart rate was measured every minute by ear lobe oximetry (Boso Puls-Meter, Bosch & Sohn GmbH, Jungingen, Germany) except at two and five minutes when the electrocardiogram was used to measure both heart rate and QTc interval. Blood pressure was measured at two and five minutes.

The electrocardiogram (for heart rate and QTc interval), blood pressure, and venous sampling for assay of plasma potassium and glucose concentrations were carried out in this order at 10, 20, 30, 40, 80, 120, 160, 200, 240 minutes and at 5, 6, 7, and 8 hours after dosing. Adverse events were assessed at baseline, before dosing, and at 30, 60, 120, 240 minutes and 8 hours after dosing. This was done by verbal questioning ("How are you?") and by using a visual analogue scale for expected symptoms (headache, palpitation and tremor), plus two decoy symptoms (drowsiness and itchiness). If clinically important symptoms and/or a heart rate of >140 bpm occurred, the
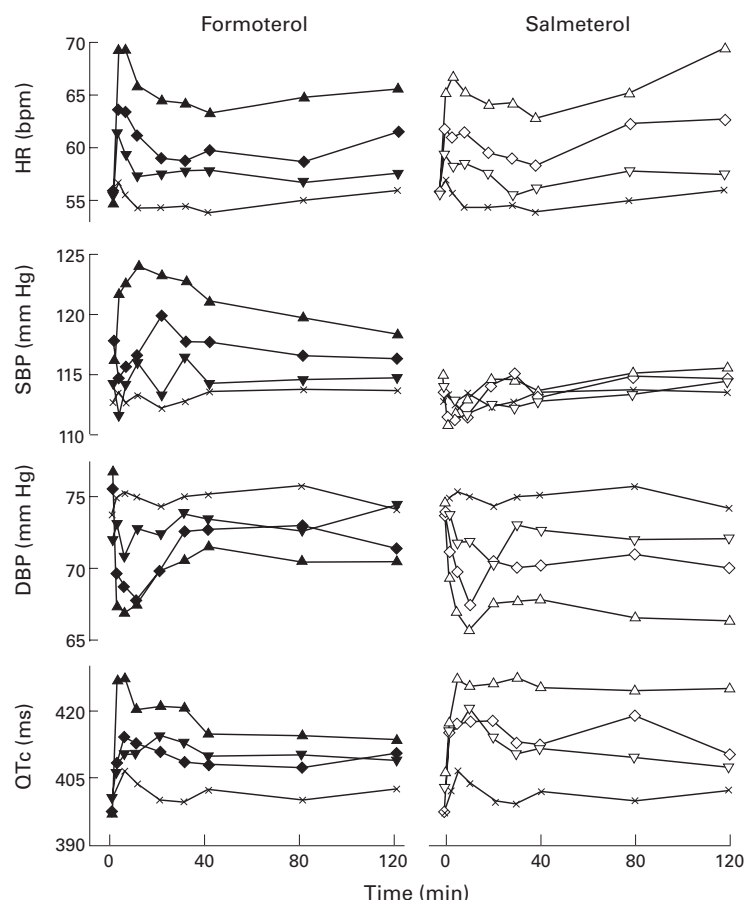
Figure 1 Mean values over the first two hours for heart rate (HR), systolic and diastolic blood pressure (SBP, DBP), and QTc interval after formoterol 24 (▼), 48 (◆), and 96 (▲) µg, salmeterol 100 (▽), 200 (◇), and 400 (△) µg, and placebo (×).
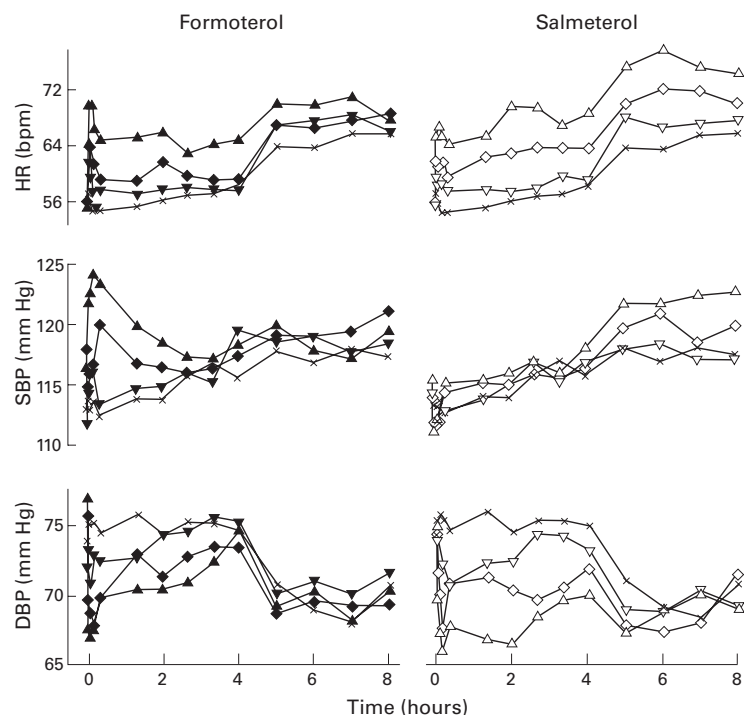

Figure 2 Mean values over eight hours for heart rate (HR) and systolic and diastolic blood pressure (SBP, DBP) after formoterol, salmeterol, and placebo. For doses see legend to fig 1. Lunch was taken after the four hour reading.

study was stopped and treatment with a β adrenoceptor antagonist considered.

ANALYSIS OF DATA

All subjects with data for at least one dose of each treatment were included in the analysis. The mean (SD) values for each outcome variable for each dose of treatment were plotted against time.

To determine relative dose potencies for predetermined outcomes we measured minimum values for plasma potassium levels and diastolic blood pressure and maximum values for heart rate, QTc interval, systolic blood pressure, and plasma glucose levels over the eight hours after dosing for each subject. Because lunch at four hours had a larger effect on some outcomes than expected, the same variables were assessed over four hours in a post hoc analysis. Mean outcome variables were plotted against log transformed dose to assess the linearity and parallelism of the log dose-response curves.[20] The relative dose potency of formoterol compared with salmeterol was calculated as the horizontal distance between parallel lines approximating the dose-response curves. The parallel lines were fitted to means obtained using an analysis of variance model including terms for subject, visit, treatment, dose, and treatment by dose interaction. The baseline (time 0) value for each outcome measure was included as a covariate in the model to allow for difference in baseline measurements between visits.

Confidence intervals (95% CI) for the relative potency were computed according to Fieller's theorem.[21] All analyses were performed using SAS for Windows 95.

Results

The analysis was carried out on data for 15 subjects who completed all visits and for one subject who completed five visits but was unable to attend for the lowest doses of formoterol and salmeterol. The 16 subjects (11 men) were aged 19–56 years. Thirteen had never smoked, one had smoked briefly, and two were current smokers.

Complete measurements are available from all time points except from three subjects who each terminated one study day early. Two subjects terminated one visit at six hours because of adverse effects following salmeterol 400 µg while the third, on formoterol 48 µg, stopped after five hours for personal reasons. All estimates of plasma potassium and glucose concentrations (n = 3080) were included in the analysis except for five serum potassium values which exceeded 6.5 mmol/l and were attributed to haemolysis. There were no differences in baseline values between treatment days (table 1).

TIME COURSE

The time course for both metabolic and cardiovascular outcome measures was markedly influenced by lunch which was always taken after the four hour reading.
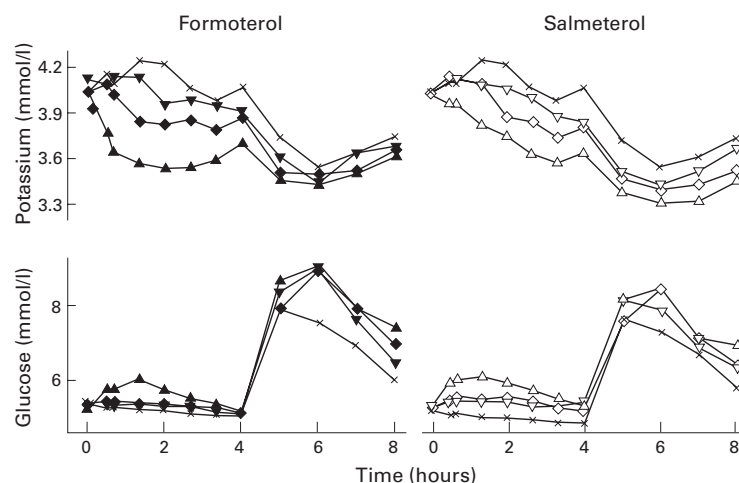
Figure 3   Mean values over eight hours for plasma potassium and glucose concentrations after formoterol, salmeterol, and placebo. For doses see legend to fig 1.
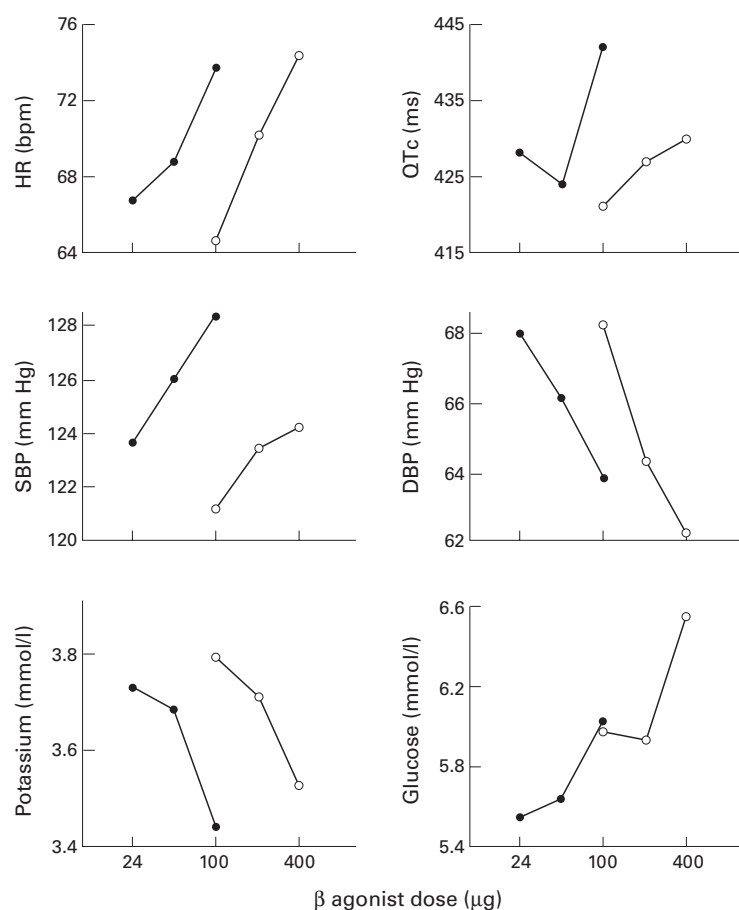

Figure 4   Dose-response curves for heart rate (HR), systolic (SBP) and diastolic (DBP) blood pressure, QTc, and plasma potassium and glucose concentrations for formoterol (○) and salmeterol (●) using mean maximum values for each dose over the first four hours (minimum for diastolic blood pressure and plasma potassium).

Heart rate and QTc interval

Both salmeterol and formoterol caused a rapid dose related increase in heart rate that was evident one minute after inhalation (figs 1 and 2). During the first 10 minutes the increase was slightly greater with formoterol than with the corresponding doses of salmeterol, but salmeterol subsequently caused a greater increase which peaked before lunch, 2–4 hours after dosing. A further postprandial increase in heart

rate occurred with both drugs which reached a maximum 5–6 hours after dosing (fig 2). The highest absolute values were seen following the highest doses of salmeterol. Dose related effects were apparent seven hours after the highest dose of formoterol and after eight hours with salmeterol.

QTc showed an early dose related increase with both drugs, in keeping with the changes in heart rate, but this was not maintained after lunch (data not given).

Systolic and diastolic blood pressure

Before lunch systolic blood pressure did not change following salmeterol compared with placebo whereas with formoterol there was an early dose related increase which gradually settled by four hours. After lunch the systolic blood pressure rose gradually in all groups but particularly in subjects taking the highest dose of salmeterol.

There was a rapid dose related fall in diastolic blood pressure after both drugs and this was more sustained after salmeterol. A further fall occurred after lunch but this was not drug related.

Metabolic response

Plasma potassium concentration showed a dose related fall following both drugs and this occurred more rapidly with formoterol (fig 3). A further fall occurred after lunch and drug related effects were still present at eight hours after salmeterol but not formoterol.

An increase in plasma glucose concentration was seen with the higher doses of both drugs but, unlike the change in plasma potassium, this occurred more rapidly with salmeterol and the effect had disappeared by four hours after both drugs. Dose related increases reappeared with both drugs after lunch and were still apparent at eight hours despite the large effect of lunch.

RELATIVE DOSE POTENCY

When the maximum (or minimum for serum potassium and diastolic blood pressure) values were related to drug dosage, formoterol was more potent than salmeterol for all outcomes after adjusting for baseline values (fig 4). The relative dose potencies (95% CI) over four hours for formoterol compared with salmeterol for heart rate, QTc interval, and diastolic blood pressure were 4.1 (3.0 to 5.6), 7.0 (2.9 to 64), and 3.3 (2.4 to 4.5), respectively. Corresponding values for plasma potassium and glucose concentrations were 5.8 (4.1 to 8.6) and 1.6 (0.7 to 2.7).

The mean relative dose potencies for formoterol compared with salmeterol over eight hours for the same variables was slightly smaller, ranging from 2.1 to 4.9 for plasma potassium concentration, heart rate and QTc interval, and diastolic blood pressure (table 2). Relative dose potencies for plasma glucose concentrations over eight hours were not calculated because the effect of lunch was considerably larger than the effect of the two drugs.

The relative dose potencies for maximum systolic blood pressure over four and eight

Table 2 Relative dose potencies (95% CI) for formoterol compared with salmeterol using mean maximal effects (minimum for diastolic blood pressure and plasma potassium concentration). Figures were calculated for the four hours before lunch and for the eight hours of the whole study

	Heart rate (bpm)	SBP	DBP	QTc interval (ms)	Plasma K$^+$ (mmol/l)	Plasma glucose (mmol/l)
Up to 4 hours	4.1 (3 to 5.6)	12.6 (No CI)	3.3 (2.4 to 4.5)	7.0 (2.9 to 64)	5.8 (4.1 to 8.6)	1.6 (0.7 to 2.7)
Over 8 hours	2.4 (1.2 to 3.8)	6.0 (2.1 to 59)	2.1 (1.0 to 3.3)	4.9 (2.0 to 16)	3.0 (1.2 to 5.7)	Not calculated

SBP, DBP = systolic and diastolic blood pressures (mm Hg)

hours were 12.6 and 6.0, respectively. Confidence intervals for systolic blood pressure could not be calculated for the four hour reading because the response to the drug differed and those for the eight hour reading were large (2.1 to 59).

ADVERSE EVENTS

Headache, palpitation, and tremor were reported more frequently with the highest dose of both drugs, with headache being the most common. Adverse effects were reported in four, five, and six subjects taking 24, 48, and 96 µg formoterol, respectively, and in three, two, and seven subjects taking 100, 200, and 400 µg salmeterol. Palpitations tended to occur at the earliest time of measurement (30 minutes), particularly with formoterol, whereas headache was more likely to be reported at four and eight hours after dosing with both drugs.

Discussion

This study compares the systemic effects over eight hours following inhalation of placebo and three doses of salmeterol and formoterol in healthy subjects. The doses of formoterol and salmeterol administered ranged from the maximum recommended dose to a fourfold higher dose to enable us to determine the therapeutic window and relative dose potency for the two drugs for the different end points. We studied normal subjects to reduce confounding factors including other medication. The study design was similar to one used previously[11] except that subjects were studied for eight hours after each dose to obtain more information on the time course of change in the different end points. Subjects had lunch after four hours and this had a larger effect on our end points than we had expected. To some extent this complicates the analysis and interpretation of our findings after the four hour measurement, although it also sheds light on how a meal affects the response to long acting β agonists.

Although salmeterol and formoterol are both long acting β$_2$ agonists with similar clinical indications, there are pharmacological differences between the drugs. Formoterol is a full rather than a partial agonist and it is less lipophilic than salmeterol,[22] which may explain its more rapid onset of action. It was anticipated, nevertheless, that the pharmacological profile of their systemic effects would be similar, thus allowing us to estimate the systemic relative dose potency of the two drugs to determine which drug, if any, had the larger therapeutic window.

TIME COURSE DATA

Within minutes of inhalation both β$_2$ agonists caused a rapid increase in heart rate and a fall in diastolic blood pressure, suggesting that a sizeable amount of drug is absorbed rapidly, presumably from the alveolar-capillary interface. This fits with previous findings that peak plasma levels of formoterol occur within five minutes of inhalation in normal subjects[23] and, in a study using oral charcoal, that most of the systemic effects from salmeterol inhaled from a metered dose inhaler are due to drug absorption from the lung.[24] The early tachycardia has been seen in previous studies[9 11 15] and is likely to be mainly caused by a direct effect on cardiac β$_2$ receptors.[25 26] The fall in diastolic blood pressure has been seen in some previous studies[9 14 15] and is attributed to β$_2$ mediated dilatation of peripheral arterioles. This fall in peripheral resistance may also contribute to the tachycardia through a reflex increase in heart rate, although we previously observed a tachycardia with salmeterol in the absence of change in diastolic blood pressure.[11] An early dose related increase in systolic blood pressure was seen with formoterol, in agreement with previous studies,[15 16] but the fact that it occurred with formoterol but not salmeterol was surprising and suggests pharmacological differences between the two drugs as discussed below.

Both formoterol and salmeterol caused an increase in the plasma glucose concentration and a fall in the serum potassium concentration as expected. During the first two hours the highest dose of formoterol had the greater effect on the serum potassium concentration whereas the highest dose of salmeterol had the greater effect on plasma glucose concentrations. Since both end points are markers of systemic activity, this again suggests pharmacological differences between the two drugs. By four hours the effects of formoterol on the plasma glucose concentration had disappeared and those of salmeterol were much reduced, in keeping with the expected effect of homeostatic mechanisms in returning glucose levels to normal. The fact that dose related effects re-emerged after lunch and were still apparent at eight hours suggests that the homeostatic mechanisms were overridden by the effects of lunch.

Both salmeterol and formoterol have sustained activity on the airways following inhalation which lasts more than 12 hours following conventional doses.[27] Studies of oral and inhaled formoterol[12 16] have suggested that the systemic activity of formoterol might be more short lived than that seen with salmeterol. Our study provides some support for this, although the effects of lunch make interpretation more difficult. In general, dose related drug effects were rather more apparent with salmeterol at both four and eight hours than with formoterol, although formoterol had some dose

related effects on heart rate at seven hours and on plasma glucose at eight hours. Part of the reason for differences in duration of effect between different end points will be differences in homeostasis, and the more rapid onset of action of formoterol may promote a more vigorous homeostatic response.

RELATIVE DOSE POTENCY OF FORMOTEROL AND SALMETEROL

Assessing the relative dose potency of two drugs from their respective dose-response curves assumes that the dose-response curves are parallel and that the drugs have similar pharmacological activity. Differences in the pharmacological profile of the two drugs for systolic blood pressure meant that relative dose potency could not be determined at four hours and the confidence intervals at eight hours were wide; it also caused some variation in relative dose potencies for other end points. Because lunch had a larger effect on the outcome variables than expected, we carried out a post hoc analysis of the four hour data in addition to the a priori analysis of the eight hour data. We have presented both since the four hour data accord better with conventional pharmacological analysis of relative dose potency, whereas it can be argued that the eight hour data may be more relevant to the everyday use of β agonists.

Formoterol was more potent than salmeterol for all end points in both analyses with relative dose potencies for our two main outcome measures (heart rate and plasma potassium concentration) of 4.1 and 5.8 for the four hour data and 2.4 and 3.0 for the eight hour data. The lower values for the eight hour data reflect the more prolonged systemic effects of salmeterol than of formoterol. The fourfold difference in the recommended doses of salmeterol and formoterol (50 μg salmeterol versus 12 μg formoterol twice daily) is close to their relative dose potency for systemic end points at four hours.

The pattern of pharmacological activity of salmeterol and formoterol showed some unexpected differences with formoterol having a larger effect on systolic blood pressure and an earlier effect on plasma potassium concentration before lunch and salmeterol having a somewhat earlier and greater effect on plasma glucose concentration. Since the effects were largely dose related it seems unlikely that they are due to chance, and the most likely explanation is differences in pharmacological activity between the two drugs. In a previous study a greater fall in the serum potassium level was seen with formoterol than with salmeterol which was attributed to the fact that formoterol is a full agonist.[17] Although this may be a factor in our study, formoterol did not have a consistently greater effect on the different end points. Both salmeterol and formoterol are highly β_2 selective agonists,[22] although both have some β_1 agonist activity[28 29] and possibly some activity on the β_3 receptor[28 30] which is thought to mediate negative chronotropic effects. There have been few direct comparisons of the two drugs but salmeterol was marginally more β_2 selective than formoterol in a guinea pig model, although both were considerably more β_2 selective than salbutamol.[29] The early increase in systolic blood pressure with formoterol but not salmeterol is particularly surprising since formoterol had some α_1 receptor blocking activity in guinea pigs.[31] The most likely explanation is that formoterol has a greater effect on cardiac β_1 receptors; alternatively, there may be differences between the two drugs on cardiac β_3 or the recently described β_4 receptors,[32] although we know of no direct evidence for this and the function of these receptors is still not fully determined. The slower rise in glucose and early fall in plasma potassium concentrations would be consistent with greater insulin release with formoterol, although plasma insulin concentration was not measured. If the increase in insulin was due to a direct effect of formoterol, it would suggest increased activity on β_2 receptors or, again, α_2 blocking activity rather than the α_1 effects that have been observed with formoterol.[29] Further work is needed to unravel the mechanisms underlying these differences between the two drugs.

The higher doses used in this study were four times the maximum recommended doses for these drugs in regular use. They are not directly relevant to current clinical practice for salmeterol but are of some relevance to formoterol now that the drug is available for relief medication up to a maximum dose of 54 μg/day. The study was carried out in healthy subjects and there is some evidence to suggest that systemic effects from inhaled β_2 agonists may be greater in healthy subjects than in patients with asthma.[9 11] The magnitude of the changes seen with the highest doses of the two β agonists was either similar or less than that seen as a result of lunch, but the two were additive and safety will relate to the effect of a drug on top of other activities such as meals and exercise. Our data show that both drugs have a relatively modest therapeutic window and this will have to be borne in mind before any move is made to increase the dose or alter the indications for use.

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